AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 10: Obesity

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U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

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Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 4 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the five topics for which (1) preliminary phase III data for drugs, phase II or III data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled by May 16, 2013, in this priority area; *and* (3) we received six to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (Nine topics in this priority area were being tracked in the system as of May 18, 2012.) The asterisks indicate the topics emerged as having higher-impact potential on the basis of expert comments and assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 10: Obesity

Topic	High-Impact Potential
1. Aspiration system (AspireAssist) for treatment of obesity	No high impact potential at this time
2. *Controlled-release phentermine-topiramate (Qsymia) for treatment of obesity	Moderate
3. *Intragastric dual balloon (ReShape Duo) for treatment of obesity	Lower end of the high-impact-potential range
4. *Liraglutide (Victoza) for treatment of obesity	Moderate
5. *Lorcaserin (Belviq) for treatment of obesity	Moderate

Discussion

According to a 2013 report from the National Center for Health Statistics, about 68% of American adults are overweight or obese, which is defined by an excess accumulation of body fat. Development of obesity was at one time thought to be simply a product of caloric intake that exceeded energy expenditure. However, researchers now know that other factors including genetics, metabolism, behavior, environment, culture, and socioeconomic status contribute to obesity's development. Obesity is associated with mortality and comorbidities including type 2 diabetes mellitus (T2DM), coronary heart disease, dyslipidemia, cardiometabolic syndrome, hypertension, stroke, sleep apnea, osteoarthritis, gall bladder disease, and some cancers.

Body mass index (BMI), according to the National Institutes of Health, is a measure of an individual's weight relative to his or her height (kg/m^2); it is significantly correlated to the body-fat percentage of an individual and is used as an easy measure to determine whether someone is overweight or obese. Patients with BMIs of 25 kg/m^2 or more are considered to be overweight, and patients with BMIs of 30 kg/m^2 or greater are considered to be obese. Obesity is further classified as extreme or morbid in patients with BMIs of 40 kg/m^2 or more.

Studies suggest that high BMI is associated with an increased mortality risk. A collaborative analysis published in The Lancet in 2009 found that in 57 prospective studies that included nearly 900,000 adults, overall mortality was lowest in adults with BMIs of 22.5–25.0 kg/m^2 and that for every 5 kg/m^2 increase in BMI over 25 kg/m^2, all-cause mortality rose by about 30%.

According to the 2009–2010 National Health and Nutrition Examination Survey, the U.S. age-adjusted mean BMI was about 29 kg/m^2 for men and women. In the 2-year cycle from 2009 to 2010, the age-adjusted obesity prevalence was about 36% among adult men and women. The American Heart Association reported in 2011 that among children and adolescents aged 2–19 years, one in three is overweight or obese and that overweight adolescents have a 70% chance of becoming overweight adults.

Non-Hispanic blacks have the highest age-adjusted obesity rates (49.5% are obese), followed by rates for Mexican Americans (40.4%), Hispanics (39.1%), and non-Hispanic whites (34.3%). According to a 2012 report from the U.S. Centers for Disease Control and Prevention (CDC), non-Hispanic black and Mexican-American men with higher incomes are more likely to be obese than are Non-Hispanic black and Mexican-American men with low income. Low-income women are more likely to be obese than are high-income women. CDC reported that prevalence of obesity in adults has increased across all income and education levels.

A 2009 study by Finkelstein and colleagues estimated total annual U.S. medical costs associated with obesity to be $147 billion and individual medical costs to be $1,429 higher for obese people than for individuals of normal weight.

Only one surgical treatment (gastric bypass surgery) has definitively demonstrated long-term efficacy for patients who are morbidly obese, and until recently, orlistat was the only U.S. Food and Drug Administration (FDA)-approved antiobesity pharmacotherapy available for long-term use in the United States. Surgery carries significant risks of morbidity and mortality, and drug therapy can have undesired side effects and limited efficacy in achieving sufficient weight loss. Additional treatment options are highly desired. Some new options are in development but have had a long and sometimes circuitous path to marketing approval.

In September 2011, concerns over the lack of effective pharmacotherapies for treating obesity drove the U.S. Congressional Committee on Appropriations to direct FDA to develop a pathway, by March 30, 2012, to support antiobesity-treatment development. That prompted FDA to work more closely with manufacturers, eventually leading to the summer 2012 approvals of the two following antiobesity drugs, which are addressed in this report:

- Combination phentermine-topiramate (Qsymia®, Vivus, Inc., Mountain View, CA)
- Lorcaserin (Belviq®, Arena Pharmaceuticals, Inc., San Diego, CA)

Additionally, liraglutide (Victoza®, Novo Nordisk a/s, Bagsvaerd, Denmark), an FDA-approved drug for managing T2DM, has gained interest for use in treating obesity. A temporary-placement gastric dual-balloon device that is inserted endoscopically is also in development for obesity treatment. Experts commenting on these four topics rated them differently, basing their opinions on the available data on efficacy and side effects.

Experts rated the three drug topics as having a moderate potential for high impact, considering available information on safety, efficacy, and diffusion. With the arrival of lorcaserin and

phentermine-topiramate to the market, it has become a priority for their manufacturers to optimize patient accessibility to treatment by addressing pricing and reimbursement barriers and prescribing limitations. Since the time of expert review, Vivus has made progress towards reducing access barriers to phentermine-topiramate; however, the latest reports indicate that drug sales are less than expected. Lorcaserin has been scheduled as a Schedule IV drug, lifting the potential prescribing limitations that were being considered at the time of expert review. It is still too early to determine how lorcaserin will diffuse among eligible patients with obesity. Liraglutide, which is already on the market for treating diabetes, might face fewer accessibility issues than lorcaserin and phentermine-topiramate and could present an opportunity to simplify treatment for the large proportion of patients who are both diabetic and obese. However, because widespread off-label use of liraglutide for treating obesity has already been documented, the overall impact of the drug should it gain market approval might not be large. The cost of liraglutide at the dosage used to treat obesity is expected to be greater than the cost for lorcaserin or phentermine-topiramate, and pricing for each drug might change, given the shared market and likelihood for competition. Experts would like to see trials directly comparing the new antiobesity medications to provide more substantiated information on their relative safety and efficacy.

Controlled-Release Phentermine-Topiramate (Qsymia) for Treatment of Obesity

- **Key Facts:** Phentermine-topiramate is a controlled-release formulation of two separate FDA-approved drugs; the drug combination acts on the central nervous system as an appetite suppressant. Phentermine is a central norepinephrine-releasing drug that was approved by FDA in 1959 as an appetite suppressant for short-term (3 months or less) obesity treatment at a dosage of 37.5 mg/day. Topiramate is a gamma aminobutyric acid agonist that FDA approved in 1996 for treating epilepsy at a dosage of approximately 400 mg/day, and it has been known to have weight loss as a side effect. Phentermine-topiramate in combination promotes weight loss while purportedly avoiding side effects caused by high doses of either drug. FDA approved the drug on July 17, 2012, on the basis of two completed, phase III trials. The reported weight loss achieved on average was between 9% and 10% of body weight. The recommended prescribing by the manufacturer includes an initial low-titration dosage and a mid-titration dosage: a 14-day starting daily dosage of 3.75 mg phentermine and 23 mg topiramate and mid-titration (maintenance) daily dosage of 7.5 mg phentermine and 46 mg topiramate for 30 days. The company has two introductory pricing programs to support diffusion that provide the initial 14-day dosage for free, reported to be a savings of $65, and a 30-day pricing strategy for the recommended mid-titration dose of $75, reported to represent a savings of $85. Thus, without these programs, the reported cost after the 14-day introduction is about $160 per month. The online U.S. drug pricing resource GoodRX lists pricing for 30-day supplies ranging from $149.99 to $159.99 at various pharmacies. Some health insurance companies and pharmacy benefit management companies have added the drug to their formularies requiring prior authorization and brand-level copayments and may limit the number of 30-day supplies covered. Coverage also depends on the insured individual's benefit level.
- **Key Expert Comments:** Experts generally expressed optimism about this intervention's ability to meet the need of patients who are obese for a medical solution for moderate weight loss, given the lack of pharmacotherapy interventions and failure of dietary and lifestyle modification programs. Experts generally indicated that both patient and clinician

acceptance would be high for this drug because the potential to eliminate long-term sequelae of obesity-related diseases is critically important. However, experts opined that the increase in per-patient costs of care might serve as a barrier to acceptance for some patients because payers generally have not reimbursed for antiobesity drugs. However, if the medication can lead to sufficient weight loss to reduce comorbidities such as T2DM, third-party payers may be willing to add the drug to their formularies.

- **Potential for High Impact:** Moderate

Intragastric Dual Balloon (ReShape Duo) for Treatment of Obesity

- **Key Facts:** Gastric bypass and some other types of bariatric surgery are the only treatments that have been demonstrated to be effective for weight loss by patients who are morbidly obese and have not had success with conservative treatments (e.g., diet, exercise). However, some patients who are super-morbidly obese are ineligible for surgery because of surgical risks and complications related to their weight. The ReShape Duo® dual intragastric balloon device (ReShape Medical, Inc., San Clemente, CA) might offer a nonsurgical alternative to such patients. According to the manufacturer, by occupying space in the stomach, the dual intragastric balloon purportedly causes patients to reach satiety with less food intake. For device placement, a clinician delivers ReShape Duo to the patient's stomach through the patient's mouth via an endoscope and guidewire. The uninflated balloons are advanced into the stomach with the guidewire and, once in the stomach, are inflated individually with equal volumes of saline. Device placement is a 15–30 minute outpatient procedure that requires only conscious sedation. The Reshape Duo is designed to be kept in the stomach for 6 months and then removed, using an endoscopic procedure similar to balloon placement. ReShape Duo is being investigated in a pivotal clinical trial of patients with BMIs between 30 and 40 kg/m^2. The company has not indicated when it will seek FDA marketing approval. ReShape Duo has been Conformité Européene (CE) marked since 2007 and, after some product revisions, was launched in the United Kingdom in March 2012. In the United Kingdom, ReShape Duo and its associated procedure reportedly cost £4,450, an equivalent to $6,814 in June 2013.
- **Key Expert Comments:** Overall, experts thought that ReShape Duo has potential to fulfill a large unmet need for patients who are obese and have unsuccessfully tried lifestyle and pharmacotherapeutic approaches to weight loss or who are ineligible for bariatric surgery or both. The device could be used in two ways: to make super-obese patients eligible for gastric bypass surgery or to offer an option to patients who are obese and do not want to undergo bypass surgery but need to lose weight. However, experts agreed that available data at this time are insufficient to determine whether ReShape Duo is safe and effective. The potential for fewer complications, reversibility, and ease of the intragastric balloon procedure compared with bariatric surgery were highlighted by experts as factors that patients and clinicians would view positively. Use of the ReShape Duo could be integrated into hospitals with minimal impact on health care processes because the procedure can be performed in existing endoscopy or outpatient surgical suites, experts agreed. But they also pointed out that the availability of a nonsurgical, endoscopic treatment option for obesity could increase the number of patients seeking care, which might necessitate an increase in staffing requirements.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Liraglutide (Victoza) for Treatment of Obesity

- **Key Facts:** Liraglutide (Victoza) is a synthetic analog of the peptide hormone glucagon-like peptide-1 (GLP-1), which is recognized (Astrup et.al., 2009) for its ability to suppress appetite and energy intake as well as delay gastric emptying; therefore, it is thought to induce a feeling of satiety. Liraglutide is engineered to have a substantially longer half-life than endogenous GLP-1 (13 hours, 1–2 minutes, respectively). Liraglutide is already approved to treat T2DM, and given the paucity of effective obesity treatments, interest is high in liraglutide as a potential weight-loss treatment that acts independently of the patient's diabetes status. Liraglutide is under investigation in a four-part phase III clinical trial (SCALE). In clinical trials, the drug is being administered at a dosage of 3 mg daily in a 6 mg/mL, 3 mL FlexPen® for subcutaneous injection.
- **Key Expert Comments:** Experts generally had a positive view of liraglutide as an obesity treatment, noting its potential to improve patient adherence to therapy recommendations and simplify treatment for patients who are obese and have diabetes. But one expert expressed concern that liraglutide could enable patients to eat liberally rather than make healthy lifestyle changes. Experts pointed out that wide use of liraglutide could be limited by both its cost and worse gastrointestinal side effects than side effects observed with the dosage used to treat diabetes, because the drug is used at higher doses for obesity treatment. One expert expressed some concern over the need for patients to self-administer the drug using an injector pen; however, most experts agreed that patients would require minimal education and that the mode of administration would be unlikely to deter liraglutide use if it demonstrates safety and efficacy in clinical trials. Experts thought that liraglutide's availability for treating obesity might reduce hospitalizations for bariatric surgery or for treating obesity-related morbidities if it can reduce the number of patients seeking surgical intervention or mitigate development of comorbidities.
- **Potential for High Impact:** Moderate

Lorcaserin (Belviq) for Treatment of Obesity

- **Key Facts:** Lorcaserin selectively stimulates the 5-hydroxytryptamine type 2C (5-HT2C) serotonin receptors in the brain, which are involved in controlling appetite and metabolism. FDA approved the drug on June 27, 2012, on the basis of three completed phase III trials. The approved indication is "as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial [BMI] of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)." The drug has been classified by the U.S. Drug Enforcement Administration as a Schedule IV drug; it became available for prescribing in June 2013. To aid diffusion, the company is offering special pricing programs in which patients can receive a 15-day free supply, for a reported savings of $100 (50% off the first month). Patients are eligible for savings of $75 per month if their health insurance copayment or out-of-pocket expense is greater than $50.
- **Key Expert Comments:** Experts thought that available clinical data indicated lorcaserin seemed promising but that postmarket studies and studies directly comparing lorcaserin to other available antiobesity pharmacotherapies are needed. Experts anticipate moderate diffusion of lorcaserin among eligible candidates, noting that the history of other antiobesity drugs such as FenPhen and sibutramine could make some patients or clinicians hesitant to use it. Lorcaserin is not expected to disrupt health care processes; instead, some experts

proposed it could reduce both the cost and care burden of treating obesity-related complications if it proves to be safe and efficacious in the long term.

- **Potential for High Impact:** Moderate

Obesity Interventions

Controlled-Release Phentermine-Topiramate (Qsymia) for Treatment of Obesity

Unmet need: The increasing prevalence of overweight and obese populations in the United States has generated a demand for novel pharmacologic therapies aimed at weight reduction and maintenance when diet and exercise have failed. However, concerns over potential adverse events associated with antiobesity pharmacotherapies significantly increased the regulatory bar for gaining U.S. Food and Drug Administration (FDA) approval—specifically regarding preapproval safety data and postmarket safety evaluation. Until about 1 year ago, orlistat, a pancreatic lipase inhibitor that blocks about one-third of daily fat absorption, was the only FDA-approved antiobesity drug available for long-term use in the United States; it remains the only one approved for adolescent use. Many patients discontinue treatment with orlistat because of its unpleasant side effects of oily spotting, flatulence, and fecal urgency. Phentermine-topiramate (Qsymia®, formerly Qnexa®) provides a new option for obese patients seeking medical therapy for weight loss.

Intervention: Phentermine-topiramate is a controlled-release formulation of two separate FDA-approved drugs. This drug combination acts on the central nervous system as an appetite suppressant.[1] Phentermine is a central norepinephrine-releasing drug that was approved by FDA in 1959 as an appetite suppressant for short-term (3 months or less) treatment of obesity at a dosage of 37.5 mg daily.[2,3] Topiramate is a gamma aminobutyric acid agonist that was approved by FDA in 1996 for treating epilepsy at a dose of approximately 400 mg/day and has been known to have weight loss as a side effect.[2,3] Topiramate was studied as a monotherapy for treating obesity; however, dose-dependent neuropsychiatric adverse events precluded further study.[2] By combining the effects of a low dose of each medication in a single treatment, phentermine-topiramate promotes weight loss while purportedly avoiding side effects potentially caused by high doses of either drug.

The new combination drug is administered daily as an oral medication.[1,4] Commercially, phentermine plus topiramate is available at four different dose levels: a low dose of phentermine 3.75 mg plus topiramate 23 mg, a middle dose of phentermine 7.5 mg plus topiramate 46 mg, a three-quarter titration dose of phentermine 11.25 mg plus topiramate 69 mg, and a high dose of phentermine 15 mg plus topiramate 92 mg.[5]

Clinical trials: In 2013, Davidson and colleagues announced results of a 56-week, randomized, double-blind, placebo-controlled multicenter phase III trial (CONQUER) that evaluated the changes in cardiovascular risk factors in patients with dyslipidemia and/or hypertension.[4] Patients with body mass indexes (BMIs) of between 27 and 45 kg/m^2 were randomly assigned in a 2:1:2 ratio to receive once-daily treatment with placebo, 7.5 mg phentermine (PHEN)/46 mg topiramate extended-release (TPM ER), or 15 mg PHEN/92 mg TPM ER. All patients received lifestyle modification counseling. The authors of the study reported the following:[4]

> PHEN/TPM ER produced significantly greater dose-related mean percentage weight loss compared with placebo in the subgroups of participants with dyslipidemia and those with hypertension. Regardless of treatment group assignment, participants with dyslipidemia who lost ≥5% of their baseline weight experienced significantly greater reductions in triglycerides (-14.5% to -39.8%), and in non-high-density lipoprotein cholesterol (-9.4% to -14.8%) than those losing <5% of their weight ($p < 0.05$). Similarly, participants with hypertension at baseline showed reduced systolic blood pressure by -7.5 to -11.8 mm Hg ($p < 0.001$ vs those with <5% weight loss). In conclusion, the dose-related weight loss induced by PHEN/TPM ER treatment was accompanied by significant improvements in cardiovascular disease risk factors in participants who had dyslipidemia or

> hypertension at baseline, suggesting that facilitating weight loss by augmenting lifestyle changes with pharmacotherapies may decrease the risk for cardiovascular disease in obese and overweight patients with co-morbidities.

In 2011, Kushner and colleagues announced results from a phase III clinical trial (SEQUEL) evaluating the safety and efficacy of phentermine-topiramate in 675 patients with BMIs of between 27 and 45 kg/m^2 and two or more obesity-associated comorbidities. This study is an extension of the CONQUER trial. Authors reported the following:[6,7]

> Patients treated with [Qsymia] had significant, sustained weight loss compared to those in the placebo group over two years. Average weight loss at week 108 was -9.3% and -10.5%, respectively, for the mid- and top-dose as compared to -1.8% for the placebo group (lease-squares mean ITT-LOCF [intention to treat–last observation carried forward]). [Qsymia] patients had improved cardiovascular and metabolic risk factors and a decrease in the need for associated medications in comparison with the placebo group. Placebo patients had a three times greater likelihood to progress to type 2 diabetes mellitus (T2DM) compared to subjects receiving top-dose [Qsymia] and a two times greater likelihood than patients on mid-dose [Qsymia].

In 2011, Allison and colleagues announced results from a 56-week clinical trial (EQUIP) evaluating the safety and efficacy of phentermine-topiramate in 1,267 patients who were morbidly obese. The authors reported the following:[8]

> Least-squares (LS) mean weight loss for phentermine-topiramate patients who completed the EQUIP study was 14.4% and 6.7% with top-dose phentermine-topiramate and low-dose phentermine-topiramate, respectively, compared to 2.1% in the placebo group ($p<0.0001$); in the ITT-LOCF analysis, LS mean percent weight loss at week 56 was 10.0% and 5.1% for the top and low dose, respectively, as compared to 1.6% for the placebo group ($p<0.0001$).[8]

The authors also reported that among patients who completed top-dose treatment of phentermine-topiramate, the following losses were observed:[8]

- 83.5% lost 5% or more of their baseline weight
- 67.7% lost 10% or more of their baseline weight
- 48.1% lost 15% or more of their baseline weight

Common adverse events reported in this study were paresthesia (tingling), dysgeusia (taste alteration), and xerostomia (dry mouth).[8] FDA has required the manufacturer to conduct 10 postmarketing requirements, including a long-term cardiovascular outcomes trial to assess the effect of phentermine-topiramate on the risk of patients developing major adverse cardiac events, such as heart attack and stroke.

Manufacturer and regulatory status: Vivus, Inc., of Mountain View, CA, makes phentermine-topiramate. FDA approved the drug on July 17, 2012, basing its decision on two completed phase III trials. The approved indication is as "an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 or greater (obese), or 27 or greater (overweight) in the presence of at least one weight-related comorbidity, such as hypertension, type 2 diabetes mellitus or high cholesterol (dyslipidemia)."[9]

FDA required a Risk Evaluation and Mitigation Strategy (REMS) for phentermine-topiramate approval, informing prescribers and "female patients of reproductive potential" of potential risks associated with the drug, including fetal orofacial cleft development during the first trimester of pregnancy, the need for pregnancy preventive practices for females of reproductive potential, and

immediate drug discontinuation in event of pregnancy.[9] Additionally, the "REMS program includes a Medication Guide, Healthcare Provider training, distribution through certified pharmacies, implementation system and a time table for assessments."[9]

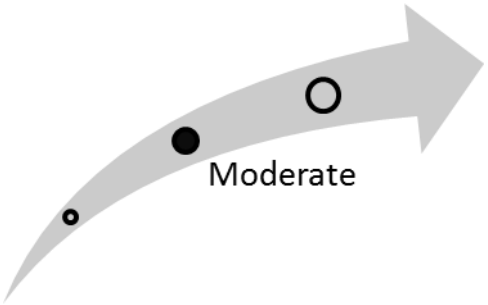
Diffusion: On September 17, 2012, this drug became commercially available in the United States,[10] with its limited distribution system posing a major barrier to diffusion.[11] Patients' out-of-pocket costs for phentermine-topiramate initially ranged from $120 to $185 per month,[5,12] raising concerns because of lack of coverage by third-party payers and high out-of-pocket costs for patients.[11] However, in December 2012, the drug was added to a number of health plan formularies; coverage depends on the insured's benefit level. The prescription typically requires prior authorization and, for some insurers, limits on the number of 30-day prescriptions offered. With copayments and manufacturer incentive programs, the expected average out-of-pocket cost to a patient is about $50–$60 per month.[13] The company's two introductory pricing programs provide the initial 14 day dosage for free, reported to be a savings of $65, and a 30-day pricing strategy for the recommended mid-titration dose of $75, reported to represent a savings of $85. Thus, without these programs and without insurance, the reported cost to a patient after the initial 14-day treatment is about $160 per month. As of June 2013, the online U.S. drug pricing resource GoodRX listed pricing for 30-day supplies ranging from $149.99 to $159.99 at various pharmacies.

In April 2013, FDA approved the REMS modification for phentermine-topiramate, allowing access to the drug through certified retail pharmacies, rather than offering it exclusively through certified mail-order pharmacies. The expanded distribution capabilities were anticipated to be in place by July 2013.[14] Also in April 2013, phentermine-topiramate was added to the Medco Health Solutions national formulary, which could have wider implications for patients' access.[15] Continued reimbursement progress is anticipated for phentermine-topiramate.[15] Diffusion could also be hastened by physicians' ability to prescribe phentermine and topiramate separately and off label to significantly mitigate patient out-of-pocket expenses. Phentermine-topiramate's main anticipated market competitor is lorcaserin, a 5-hydroxytryptamine type 2C (5-HT2C) receptor agonist that selectively stimulates the 5-HT2C serotonin receptors in the brain, which are involved in controlling appetite and metabolism.[16]

Clinical Pathway at Point of This Intervention

Patients are usually evaluated for obesity in a primary care setting in which clinicians take height and weight measurements to calculate BMI. Individuals with BMIs of 30 kg/m^2 or more are classified obese. Obese individuals are screened for other comorbid conditions, such as diabetes and hypothyroidism, that may influence treatment decisions and outcomes.[17] A patient's other medication use must also be assessed because some drugs, such as oral contraceptives, certain antipsychotics, and antidiabetes medicines, may interfere with weight loss or contribute to excessive weight gain.[18] Patients with BMIs of 30 kg/m^2 or more or BMIs of 25 kg/m^2 or more with comorbid obesity-related risk factors or diseases (e.g., hypertension, dyslipidemia, coronary heart disease, T2DM, sleep apnea) may be candidates for drug therapy.[18] Drug therapy is typically offered in conjunction with a program of physical activity, nutrition counseling, and behavior management.

Figure 1. Overall high-impact potential: phentermine-topiramate (Qsymia) for treatment of obesity



Experts commenting on this drug combination expressed optimism about its ability to meet the need for treatments for patients who are obese, given the lack of medical interventions for treating obesity and the average amount of weight loss reported in preliminary studies. Experts generally indicated that both patient and clinician acceptance would likely be high for this intervention, because the potential to eliminate long-term sequelae of obesity is critically important. However, costs and lack of insurance coverage could be barriers to adoption by some patients and could create health disparities between those who can and cannot afford the drug. Although preliminary results are promising, further studies evaluating efficacy and safety and comparing it to other, newly approved antiobesity medications are needed, experts opined. Overall, experts agreed that antiobesity pharmacotherapies might serve as an effective alternative to surgery for some patients who are obese. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on phentermine-topiramate.[19-25] We organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Antiobesity medications have a high potential to address a significant unmet need, the experts generally agreed. "There is a significant gap in obesity treatment care for those patients who do not qualify for bariatric surgery but still need help beyond lifestyle measures alone," one clinical expert commented. "Adjuvant medications are limited at present. Additional medications which are safe could help to fill this gap."[21]

Patient health outcomes have moderately high potential to significantly improve with use of phentermine-topiramate, the experts generally agreed, with one stating, "There have been a number of studies of [Qsymia] each of which shows a weight loss of between 5 and 15% from baseline. This seems quite significant."[22] Experts remained optimistic about preliminary trial results, although some would like to evaluate long-term, safety trial results before comprehensively assessing this drug's potential health outcomes. However, basing their opinions on the results from the preliminary studies, experts believe phentermine-topiramate holds strong promise compared with the promise of other antiobesity drugs under development or recently approved.

Acceptance and adoption: The potential for clinician and patient acceptance of an effective antiobesity medication is moderately high, the experts generally agreed. Uncertainty about long-term adverse events is a potential barrier to patient acceptance, several experts noted, but one expert opined that patients would acceptingly adopt "a pill, with minimal side effects, and a potential for a 10% weight loss."[22]

Cost might slow acceptance. Please note that at the time the experts commented, phentermine-topiramate coverage had not yet been established by any third-party payers. Coverage as a drug

requiring prior authorization with a brand copayment substantially reduces estimated monthly out-of-pocket costs for patients with insurance that covers the drug, from about $160 to about $60.[13]

Several experts highlighted the fact that antiobesity pharmacotherapy is typically not covered by third-party payers and thought that patients would bear the costs out of pocket. However, recent positive coverage changes may indicate that payers are looking at antiobesity drugs differently now because of the known obesity-related comorbidities. Several experts believe the potential health outcomes far outweigh the financial costs, if a patient can afford the cost. Reducing or eliminating long-term complications from obesity might ultimately reduce per-patient costs over time, a majority of experts thought. Several experts indicated that initial costs of using these pharmacotherapies might be lower than the cost of undergoing bariatric surgery or other antiobesity surgical interventions.

Health care delivery infrastructure and patient management: As an oral drug, this drug would not significantly disrupt the health care delivery infrastructure, a majority of experts agreed. But several opined that antiobesity pharmacotherapies might reduce the need for bariatric surgery in some patients, thus disrupting the current health care model for this patient population. On the other hand, it might also make severely obese patients eligible for surgery who were not previously eligible, another possible disruption.

Health disparities: Experts generally agreed that costs associated with antiobesity pharmacotherapies and many third-party payers' unwillingness to cover these drugs might serve as barriers to access for uninsured and low-income patient populations and, thus, increase health disparities related to obesity. Please note that since the experts commented, the major pharmacy benefit manager Medco Health Solutions added phentermine-topiramate to its national formulary in a tier 3 position, which will result in patient copayments of $50–$60 per month, depending on benefit design.[15]

Intragastric Dual Balloon (ReShape Duo) for Treatment of Obesity

Unmet need: Although bariatric surgery is considered an effective intervention for obesity, it is an invasive procedure with risks and side effects. Because of this, it is indicated only for morbidly obese patients (BMI greater than 40 kg/m^2) or for obese patients with BMIs of 35–40 kg/m^2 who have related comorbidities. Morbidities that put patients at high surgical risk such as unstable angina and acute congestive heart failure typically preclude patients from such surgery. Therefore, a need exists for minimally invasive treatments that could enable patients who are super-obese to lose 5% to 10% of their excess body weight. Less-invasive, safer endoluminal approaches for weight loss are being investigated to potentially extend treatment to patients with high surgical risk and to patients with BMIs of less than 40 kg/m^2.[26] The ReShape Duo® is a dual intragastric balloon being investigated for nonsurgical treatment of obesity in patients with BMIs between 30 and 40 kg/m^2.

Intervention: The ReShape Duo is a dual intragastric balloon designed for nonsurgical obesity treatment. Weight loss with the Reshape Duo is achieved by reducing the stomach's capacity: the inflated dual balloon occupies space in the stomach, purportedly causing the patient to achieve satiety with less food intake.[27]

Placement of the Reshape Duo is a 15–30 minute outpatient procedure requiring only conscious sedation. The clinician delivers the dual intragastric balloons to the patient's stomach through the patient's mouth via an endoscope and guidewire. The uninflated balloons are advanced into the stomach with the guidewire and once in the stomach are inflated individually with equal volumes of saline totaling 900 cc, or 450 cc for each balloon.[27,28]

Compared to single intragastric balloons, which are inflated with 400–700 cc of saline, the dual-balloon design of Reshape Duo purportedly allows for a greater stomach volume to be occupied without overdistending it.[27] The company states that the dual balloon is also designed to conform with the stomach's natural curvature and reduce the risk of balloon migration and obstruction that is seen with single intragastric balloons.[27]

The Reshape Duo is designed to be kept in the stomach for 6 months. After that time, clinicians remove the balloons using an endoscopic procedure similar to the balloon placement. During this procedure, a clinician places the endoscope in the patient's stomach while the patient is under conscious sedation. The endoscope is fitted with a "proprietary suction cap" to drain the saline from the balloons individually in a controlled manner. Once the balloons are drained, the clinician secures the deflated dual balloon's tip with a snare on the endoscope and removes the device through the patient's mouth.[28]

In a pivotal clinical trial, the ReShape Duo is being investigated in patients with BMIs of between 30 and 40 kg/m^2.[29]

Clinical trials: In 2011, a manufacturer's press release announced results from a phase I investigational clinical study that assessed the safety and effectiveness of ReShape Duo combined with lifestyle modification in patients with BMIs of 30–40 kg/m^2.[30] The study randomly assigned 30 patients (26 women and 4 men) aged 26–59 years across 3 different sites to the treatment group (21 patients) or control group (9 patients) in a 2:1 ratio.[31] Patients in the treatment group received ReShape Duo through endoscopic placement and both groups underwent similar diet and exercise counseling. After 24 weeks, the device was removed from patients in the treatment group. In 2012, Ponce and colleagues reported that after 24 weeks, the mean excess weight loss in the treatment group was 31.8%±21.3% and in the control group was 18.3%±20.9% (p=0.1371).[31] The authors reported that at 48 weeks, which was 24 weeks after device removal, patients treated with ReShape

Duo maintained 64% of their weight loss.[31] In reporting on the safety of ReShape Duo, the authors reported the following:[31]

> No deaths, unanticipated adverse effects, early removals, balloon deflations, or balloon migrations occurred. In the [treatment group], 4 patients were readmitted for severe nausea, 1 had asymptomatic gastritis at balloon removal, and 1 patient experienced transient hypoxia during device removal.

Manufacturer and regulatory status: ReShape Duo is being developed by ReShape Medical, Inc., of San Clemente, CA. ReShape Duo is approved by FDA only as an investigational device.[27] ReShape Medical is sponsoring a pivotal clinical trial (REDUCE trial) investigating ReShape Duo's safety and efficacy for weight loss.[29] In February 2013, the company announced it had completed study enrollment within 6 months; enrollment included 326 patients over 8 participating sites.[30] The company has not indicated when it will seek FDA marketing approval. ReShape Duo has been Conformité Européene (CE) marked since 2007 and, after some product revisions, was launched in the United Kingdom in March 2012.[32]

Diffusion: If ReShape Duo is approved for treating obesity, it is expected to diffuse at a moderate pace as an adjunct to lifestyle modifications because it is a temporary solution. Another intragastric balloon (Garren-Edwards gastric bubble) was withdrawn from the U.S. market because of concerns about safety and efficacy, which might negatively affect how patients and clinicians view ReShape Duo.[33] At that time, the U.S. Centers for Medicare & Medicaid Services established a national coverage determination (NCD) for treating obesity using gastric balloons. The NCD indicated that "the use of the gastric balloon is not covered under Medicare, since the long term safety and efficacy of the device in the treatment of obesity has not been established."[34]

Because of this determination, intragastric balloons coming to the U.S. market might need to undergo a formal National Coverage Analysis to establish coverage under Medicare; after Medicare approval, other third-party payers often follow suit. ReShape Duo is expected to cost between $6,500 and $8,000,[35] which might make it more appealing than surgical procedures for some patients. However, diffusion of ReShape Duo is likely to be hampered if payers choose not to reimburse for its use.

For patients with BMIs between 30 and 40 kg/m^2, ReShape Duo could compete with available pharmacotherapies for obesity.[36] Weight-loss surgery is indicated for patients only after other therapies have failed or in cases in which patients are experiencing complications related to their obesity. However, these patients must have a BMI of 40 kg/m^2 or more or obesity-related comorbidities with a BMI of 35 kg/m^2 or more to be recommended for surgery.[37] Therefore, ReShape Duo will likely compete with these surgeries only in the population of patients with BMIs of 35 kg/m^2 and obesity-related comorbidities. ReShape Duo also could complement weight-loss surgeries in some patients. Bariatric surgery in patients with BMIs of 50 kg/m^2 or more can present high surgical risk and technical challenges, and these patients may benefit from preoperative weight loss.[38] If the indications for ReShape Duo include patients with BMIs this high, the device could serve as a noninvasive means for weight loss prior to bariatric surgery.

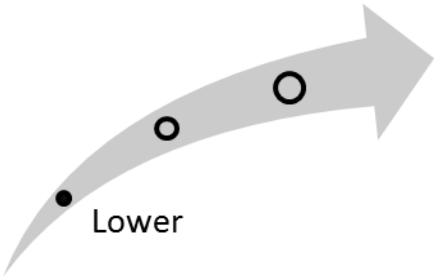
ReShape Duo may also compete with other minimally invasive endoluminal treatments that are in development, such as the EndoBarrier® endoluminal sleeve. Additionally, intragastric balloons that are approved in other nations may compete with the ReShape Duo if they receive approval in the United States.[39]

Clinical Pathway at Point of This Intervention

The National Institutes of Health's Panel on Weight Loss recommended that patients who are morbidly obese lose 10% of their excess body weight before bariatric surgery to help reduce

surgical risks and postoperative complications.[40] However, available preoperative weight loss methods have demonstrated suboptimal success in patients who are morbidly obese. Losing weight through diet and exercise alone has often not been successful in this patient population. Therefore, physicians may also recommend weight-loss medication.[40] Patients and clinicians are expected to embrace the availability of other nonsurgical options for treating obesity and/or promoting preoperative weight loss in patients who have not lost weight using conservative treatment options.

Figure 2. Overall high-impact potential: intragastric dual balloon (ReShape Duo) for treatment of obesity



Overall, experts commenting on this intervention thought that ReShape Duo aims to fulfill a large unmet need for treatments for patients who are obese and have exhausted other weight-loss methods (e.g., behavior therapy) and are ineligible for bariatric surgery. However, the experts agreed that available data are insufficient to determine whether ReShape Duo is safe and effective. An expert with a research background cautioned that a previously studied balloon for treating obesity was removed from the market because of safety and efficacy concerns. A clinical expert also pointed out that available data are inconclusive regarding whether ReShape Duo is more effective at treating obesity than behavioral therapy alone, which dampened his expectations for the intervention. This expert noted that results comparing ReShape Duo to diet and exercise (REDUCE trial) are expected in 2014 and should help gauge the overall potential for the device to fulfill the unmet need. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems and administration backgrounds, provided perspectives on this topic.[41-46] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Treating obesity remains a major health care challenge, the experts agreed, noting that few effective interventions are available for patients with the condition. Experts with research and clinical backgrounds pointed out that ReShape duo might have great potential but that available data showed no statistically significant improvement in outcomes for patients who used the device over those who underwent behavioral therapy alone. Two experts with health systems and administration backgrounds highlighted the belief that ReShape Duo could provide a nonsurgical option for patients who are obese and that the device appears to have potential to elicit weight loss in some patients. One of these experts also commented on the importance of identifying appropriate patients for ReShape Duo, such as those likely to adhere to recommended adjunctive lifestyle changes (e.g., diet and exercise).

Additional, larger studies are needed to determine ReShape Duo's potential to improve patient outcomes, the experts agreed. A clinical expert added that results from the REDUCE trial, expected in 2014, should provide more informative data on the device's efficacy.

Acceptance and adoption: According to the experts, clinicians and patients are likely to view ReShape Duo positively if it demonstrates safety and efficacy in clinical trials. In particular, experts noted the potential for fewer complications and ease of the procedure compared with surgical weight-loss methods. The procedure's reversibility is another attractive feature of ReShape Duo, one research expert mentioned. Device implantation could have fewer complications than long-term pharmacotherapy for weight loss, one expert with a systems and administration background added.

Implanting and removing the device should require minimal training, making clinician preference a possible factor affecting diffusion, most experts agreed. A clinical expert thought that a small learning curve would exist for performing physicians, especially those already familiar with endoscopic gastrointestinal procedures; this expert commented that adoption is likely to be high among these physicians but much lower among other specialists unfamiliar with gastrointestinal techniques (e.g., esophageal intubation). This expert also mentioned that adoption is likely to depend on whether payers are willing to cover the device and its procedural costs.

Health care delivery infrastructure and patient management: Use of the dual balloon is likely to have a minimal impact on health care delivery and infrastructure, the experts agreed. Some experts commented that the device should not require providers to bear major acquisition costs because it can be performed in already-existing endoscopy or outpatient surgical suites. The demand on hospital staff could increase, noted an expert with a health systems and administration background, if ReShape Duo's availability increases the number of obese patients seeking care.

One research expert proposed that ReShape Duo use might reduce the need for dedicated bariatric centers and alleviate the burden of patient monitoring often needed for bariatric patients with procedure-related nutritional deficiencies. An expert with a health systems and administration background commented that the intervention could provide an alternative to long-term pharmacotherapy and an option for preoperative weight loss. If the latter were to occur, ReShape Duo's availability could increase the number of patients eligible for bariatric surgery, as was pointed out by an expert with a research background. According to a clinical expert, given the available data, ReShape Duo is unlikely to shift standard management procedures for patients who are obese.

Health disparities: With no reimbursement information available, most experts agreed it was unclear as to whether the availability of ReShape Duo would have an effect on health disparities. Majority opinion was that a lack of coverage would limit patient accessibility to the device. Two experts with health systems and administration backgrounds agreed that ReShape Duo costs less than available surgical procedures; however, one opined that the device could improve health disparities by offering a lower-cost option but the other noted that even at a lower cost, the device is still likely to be too expensive for disparaged populations. According to a clinical expert, ReShape Duo is likely to have a minimal impact on health disparities because, as available data suggests, its clinical efficacy is not statistically significant. However, the expert added, the device has potential to increase health disparities if it proves to be effective for weight loss, because it is likely to be out of reach for most patients who cannot afford it.

Liraglutide (Victoza) for Treatment of Obesity

Unmet need: In the United States, 35.7% of adults are obese.[47] Among children and adolescents aged 2–19 years, one in three is overweight or obese and one in six is obese,[48] and overweight adolescents have a 70% chance of becoming overweight adults.[48] The increasing prevalence of overweight and obese populations in the United States has generated a call for novel pharmacologic therapies aimed at weight reduction and maintenance when diet and exercise have failed. However, concerns over potential adverse events associated with antiobesity pharmacotherapies significantly increased the regulatory bar for gaining approval—specifically regarding preapproval safety data and postmarket safety evaluation—set forth by FDA.

Until recently, orlistat, a pancreatic lipase inhibitor that blocks about one-third of daily fat absorption, was the only FDA-approved antiobesity drug available for long-term use in the United States and is still the only one approved for adolescent use. Many patients discontinue treatment with orlistat because of its unpleasant side effects of oily spotting, flatulence, and fecal urgency. Liraglutide (Victoza®) provides another option for patients who are obese and seeking medical therapy for weight loss.

Intervention: Liraglutide is an approved treatment for managing blood glucose levels in patients with T2DM.[49] Liraglutide is a synthetic analog of the peptide hormone glucagon-like peptide-1 (GLP-1) that has been shown to suppress appetite and energy intake and delay gastric emptying, which may induce a feeling of satiety.[50] Endogenous human GLP-1 has a short half-life (1–2 minutes); however, liraglutide has been modified to allow binding to serum albumin, which increases its half-life to about 13 hours.[50] It has been demonstrated to aid blood glucose control by stimulating insulin release and lowering glucagon secretion in response to high glucose levels.[50]

Liraglutide is administered once daily via subcutaneous injection using an automatic injection pen. In clinical trials, liraglutide is being self-administered in daily doses ranging from 1.2 to 3.0 mg.[50]

Clinical trials: Liraglutide's manufacturer is investigating the drug in a four-part, phase III randomized controlled trial, SCALE™ (Satiety and Clinical Adiposity-Liraglutide Evidence in Non-diabetic and Diabetic people).[49] The trial includes more than 5,000 patients who are either overweight (BMIs of 27 kg/m^2 or more) with comorbidities (e.g., hypertension, dyslipidemia, T2DM) or obese (BMIs of 30 kg/m^2 or more). In the first SCALE trial (SCALE Maintenance) 422 patients were pretreated with a 4–12 week, low-calorie diet then randomly assigned to receive either liraglutide 3 mg daily administered in a 6 mg/mL, 3 mL FlexPen® for subcutaneous injection or placebo 3 mL daily FlexPen for subcutaneous injection. Authors reported the following:[51]

> Mean run-in weight loss for all individuals who were randomised was 6.0% (6.3 kg). After 56 weeks of treatment, liraglutide provided statistically significant improvements in all measures of weight loss change from run-in compared to placebo treatment (Table) ($p<0.0001$ in all analyses). During treatment, net weight changes post-run-in were -6.1% vs 0.1% (-5.7 kg vs +0.2 kg) for liraglutide vs placebo, respectively. Significantly more liraglutide vs placebo recipients maintained run-in weight loss and lost additional run-in weight. More than twice as many participants on liraglutide lost >5% additional run-in weight compared to those on placebo. Completion rates, serious AEs [adverse events] and withdrawals due to Aes were similar for each group. More nausea and vomiting were reported during liraglutide vs placebo treatments, occurring mainly during dose-escalation; 64% of liraglutide nausea cases were mild, and most cases declined in frequency by 4-6 weeks. Psychiatric AEs were reported by 11% and 12% of subjects in each arm, respectively.

The second trial of the series (SCALE Diabetes) was a double-blind study and involved 846 overweight or obese patients with T2DM, who were randomly assigned in a 2:1:1 ratio to receive 3 mg liraglutide, 1.8 mg liraglutide, or placebo.[49] After 56 weeks, patients discontinued treatment and were observed for a 12-week observational period.[49] A company press release reported the following results regarding weight-loss in the patient population with mean baseline weight of about 106 kg and BMI of 37 kg/m^2:[49]

> The weight loss for people treated with liraglutide 3 mg and liraglutide 1.8 mg after 56 weeks were 6% and 5%, respectively compared to a 2% weight loss for people treated with placebo. The proportion of people achieving a weight loss of at least 5% or 10% was 50% and 22% for liraglutide 3 mg, 35% and 13% for liraglutide 1.8 mg, and 13% and 4% for placebo treatment. All differences for both doses of liraglutide were statistically significantly different from placebo and the trial met all three co-primary endpoints. During the 12- week follow-up period after treatment discontinuation, people in both liraglutide treatment groups experienced a moderate weight regain…. Liraglutide was generally well tolerated and the 56-week completion rate was 77%, 78% and 66% for liraglutide 3 mg, liraglutide 1.8 mg and placebo, respectively. Withdrawals due to adverse events were below 10% in all treatment groups. In line with previous liraglutide trials, the most common adverse events were related to the gastrointestinal system and diminished over time. No other apparent differences between the treatment groups were observed with respect to adverse events and standard safety parameters.

The third trial (SCALE Obesity and Prediabetes) was a 56-week, double-blind trial evaluating liraglutide's potential to induce and maintain weight loss in nondiabetic patients.[52] Investigators randomly assigned 3,731 patients who were overweight or obese (mean baseline weight of 106 kg and BMI of 38 kg/m^2) in a 2:1 ratio to receive treatment with 3 mg liraglutide or placebo, in combination with diet and exercise.[52] A company press release reported the following:[52]

> The average weight loss for people treated with liraglutide 3 mg at 56 weeks was 8.0% compared to 2.6% for people treated with placebo. The proportion of people achieving a weight loss of at least 5% was 64% for liraglutide 3 mg and 27% for placebo. The proportion of people achieving a weight loss of at least 10% was 33% for liraglutide 3 mg and 10% for placebo treatment. All differences between liraglutide and placebo were statistically significantly different and the trial met all three co-primary endpoints.
>
> Of all people participating in the trial, 61% had prediabetes at randomisation. At 56 weeks, 69% of the prediabetes subgroup treated with liraglutide 3 mg no longer showed signs of prediabetes, compared to 33% for the placebo-treated group. Of the 39% of the people without prediabetes at randomisation, 7% of the liraglutide 3 mg treated people developed prediabetes, compared to 21% of the people in the placebo group. Both differences between liraglutide 3 mg and placebo were statistically significant…liraglutide was generally well tolerated. The 56-week completion rate was 72% and 64% for liraglutide 3 mg and placebo, respectively. Withdrawals due to adverse events were below 10% in both treatment groups. The most common adverse events were related to the gastrointestinal system and they diminished over time.

According to the press release, patients taking 3 mg liraglutide experienced statistically significant improvements in obesity-related risk factors (e.g., blood pressure) compared with the rates of those factors in patients given placebo.[52]

The fourth SCALE trial (SCALE Sleep apnoea) is a study of about 340 patients that is investigating the safety and efficacy of once-daily 3 mg liraglutide in combination with diet and exercise for reducing the severity of obstructive sleep apnea.[52]

Manufacturer and regulatory status: Liraglutide is an FDA-approved treatment for managing blood glucose levels in patients with T2DM.[49] During studies of patients with T2DM, liraglutide was found to lead to a dose-dependent weight loss, raising interest in the drug as a potential weight-loss treatment that could act independently of a patient's diabetes status.[50] According to the manufacturer, as of June 2013, liraglutide "is not approved for weight management and should not be prescribed for its treatment;" however, results from a 2011 survey (discussed below) suggest widespread off-label use of the drug for treating obesity.[49,53] The company expects to complete its pivotal SCALE trial in the third quarter of 2013 and to submit liraglutide (3 mg dose) for regulatory review as an obesity treatment in the United States and European Union "around the turn of the year."[52]

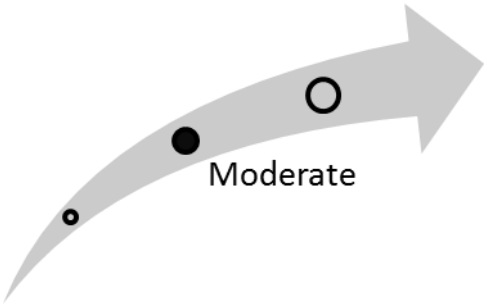
Diffusion: Given the U.S. prevalence of overweight and obesity, new antiobesity pharmacotherapy options are expected to diffuse rapidly among this population. A survey of primary care physicians published in January 2011 suggests that liraglutide and a second GLP-1 analog approved to treat T2DM, exenatide (Byetta®), are already being used off-label to treat obesity; about one-third of surveyed primary care physicians listed one of the GLP-1 analogs as the obesity drug they perceive as being most efficacious.[53] Therefore, although liraglutide is not marketed as an antiobesity treatment, this survey suggests widespread off-label use for treating obesity.[53]

Most third-party payers do not provide coverage for antiobesity medications, and those that do, typically require that a patient have a comorbid condition (e.g., hypertension, T2DM). For liraglutide, at least one third-party payer (Aetna) considers weight-loss pharmacotherapy medically necessary in the patients being treated in clinical trials.[54] If liraglutide's efficacy is demonstrated to rival or exceed that of available antiobesity drugs, third-party payers would probably reimburse its use in the appropriate patient populations. Head-to-head comparative controlled trials are needed to determine which antiobesity medications work best.

Clinical Pathway at Point of This Intervention

Individuals who are obese are screened for other comorbid conditions, such as diabetes and hypothyroidism, that may influence treatment decisions and outcomes.[17] Medication use must also be assessed because some drugs, such as oral contraceptives, certain antipsychotics, and antidiabetes medicines, may interfere with weight loss or contribute to excessive weight gain.[18] Patients with BMIs of 30 kg/m^2 or more or BMIs of 25 kg/m^2 or more with comorbid obesity-related risk factors or diseases (e.g., hypertension, dyslipidemia, coronary heart disease, T2DM, sleep apnea) may be candidates for drug therapy.[18] Drug therapy is typically offered in conjunction with a program of physical activity, nutrition counseling, and behavior management. If proved efficacious, liraglutide could represent a novel mechanism of action that provides an additional nonsurgical option to orlistat, phentermine-topiramate, or lorcaserin for overweight patients with BMIs of between 30 and 40 kg/m^2.

Figure 3. Overall high-impact potential: liraglutide (Victoza) for treatment of obesity



Experts commenting on this drug thought that liraglutide has potential to provide a nonsurgical treatment for obesity after diet and exercise strategies have failed. Most experts noted that available pharmacotherapies for treating obesity have unpleasant side effects and unknown long-term efficacy at this point. If liraglutide demonstrates safety and long-term efficacy, it could fulfill a large unmet need. Some experts who were less optimistic about liraglutide commented that "there are more effective treatment options (e.g., stomach bands)" and that the availability of other treatment options, potential cost of treatment, and possibility of treatment-emergent adverse events positions liraglutide to have "very minimal potential to fulfill the unmet needs of this market." However, one clinical expert considered liraglutide to have "a great potential to fulfill dual needs in the treatment of diabetes and obesity," and another stated that liraglutide could be "an untapped resource for obesity treatment" but that more research is needed before making conclusions about the drug. Experts noted that if liraglutide becomes available, it would provide physicians a new treatment option for a condition that historically has had very limited success with pharmacotherapy. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on liraglutide.[55-61] We organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Obesity incidence is increasing and experts agreed an important need exists for nonsurgical weight-loss options with favorable safety profiles. Most experts also recognized that patients who are obese are at risk of having many other complications, with one emphasizing the need for "a safe and effective pharmacological agent that could not only assure and maintain a healthy weight but also reduce the risk of obesity-related conditions such as high blood pressure, cardiovascular disease, type II diabetes and certain cancers." Experts thought that available clinical trial data was promising regarding liraglutide's ability to elicit weight loss; however, the general consensus was that more, longer-term studies are needed, with one research expert stating that "initial results from trials are virtually always more rosy than the long-term effects." Some experts were less concerned about the unmet need that liraglutide intends to address. A research expert stated that there is "already prevalent off-label use of this drug to treat obesity," and an expert with a health systems and administration background pointed out that other treatment methods exist (e.g., FDA-approved drugs, surgical procedures, lifestyle modification).

Some experts had reservations about using liraglutide to treat obesity—that patients might substitute a weight-loss drug for appropriate lifestyle modifications. "It is possible that a more vigorous exercise program and a more healthy diet plan would result in similar results [as liraglutide]," an expert with a research background opined. The treatment's gastrointestinal side

effects could limit its potential, most experts thought; however, one expert with health systems and administration background pointed out that "there is no information that suggests that the nausea/vomiting seriously impacted the patients' health or resulted in a big drop-out from the trials." Some experts were concerned about the potential for increased frequency or seriousness in adverse events with the dosing used to treat obesity, which is higher than dosing for the diabetes indication. However, one clinical expert noted that available clinical data suggest liraglutide is safe and associated with few side effects at the obesity dosage.

Acceptance and adoption: Liraglutide as a weight-loss option would be well-accepted by both patients and clinicians, the experts agreed. One clinical expert opined, "the minimal side effects, potential for weight loss and ease of use and small learning curve for the pen make this [liraglutide] an attractive alternative," but pointed out that daily injection could be an issue for elderly patients. One expert with a health systems and administration background thought that "an important factor to help increase patient participation with a drug requiring injection would be to have a good nurse-administered education program." Subcutaneous injection with a pen will prevent "sky-high" acceptance, one research expert thought, and most experts agreed that other notable barriers to wide acceptance of liraglutide might be high cost and the potential for increased gastrointestinal side effects at higher doses of the drug compared with such side effects at the diabetes dosage. According to another research expert, "if studies indicate clinically significant benefit over oral therapy for obesity with fewer AEs [adverse events], expect moderate acceptance among clinicians as an option before surgical intervention."

Some experts expressed concern that lorcaserin would enable liberal eating habits, which could lead to weight gain over the long term, whereas other experts commented that the drug could dually target obesity and diabetes, simplifying treatment and possibly improving adherence to treatment recommendations for many patients, notably those already taking an injectable therapy (e.g., insulin). "The ability to prescribe a medication and do appropriate follow-up could provide clinician's an opportunity to charge for an outpatient visit," an expert with a health systems and administration background suggested.

Health care delivery infrastructure and patient management: Rather than disrupt current health care delivery infrastructure, most experts thought, liraglutide has potential to alleviate the burden of treating obesity-related complications. According to one clinical expert, liraglutide could "augment the system by improving a large group of patients' outcomes. It could possibly reduce costs and hospitalizations which occur in individuals with obesity and its complications." As an option prescribed after diet and exercise has failed and before surgical intervention, liraglutide could reduce inpatient lengths of stay, the experts agreed. One research expert cautioned that liraglutide's availability might heighten the demand for injectable therapy, which could increase complications from injection errors. To this end, experts agreed that patients would require instruction on administering liraglutide using the injector pen. An expert with a health systems and administration background pointed out that this could "result in longer amount of time needed with each patient and a small disruption in how patients are currently managed." According to a clinical expert, liraglutide could emerge as a popular drug choice for treating T2DM if proven to elicit greater weight loss than standard first-line diabetes therapy (metformin), affecting care for this patient population.

Health disparities: Experts agreed that liraglutide use could improve health disparities among patients who are obese if its cost enables underserved groups, in which obesity is most prevalent, to receive treatment. However, if liraglutide is priced too high, treatment is likely to be limited to only those who can afford it, precluding those most affected by the condition from treatment and exacerbating health disparities.

Lorcaserin (Belviq) for Treatment of Obesity

Unmet need: The increasing prevalence of overweight and obese populations in the United States has generated a call for novel pharmacologic therapies aimed at weight reduction and maintenance when diet and exercise have failed. However, concerns over potential adverse events associated with antiobesity pharmacotherapies significantly increased the regulatory bar for gaining approval—specifically regarding preapproval safety data and postmarket safety evaluation—set forth by FDA. Until recently, orlistat was the only FDA-approved antiobesity drug available for long-term use in the United States and is still the only one approved for adolescent use. Many patients discontinue treatment with orlistat because of its unpleasant side effects of oily spotting, flatulence, and fecal urgency. Lorcaserin (Belviq®) provides a new option for patients who are obese and seeking medical therapy for weight loss.

Intervention: Lorcaserin (Belviq®) is a 5-H2C serotonin receptor agonist (activator) that selectively stimulates 5-H2C receptors in the brain that are involved in controlling appetite and metabolism.[16] Lorcaserin is an oral therapy intended for use in conjunction with diet, exercise, and behavior modifications in patients who are overweight or obese.

In phase III trials, lorcaserin was investigated in obese and overweight patients with a minimum of one comorbid condition. In these trials, lorcaserin was self-administered orally once or twice daily at 10 mg per dose.[62,63] The product labeling states that the drug dosage is "10 mg administered orally twice daily."[64] The drug has been classified by the U.S. Drug Enforcement Administration (DEA) as a Schedule IV drug (i.e., with a low potential for abuse and low risk of dependence); it became available for prescribing in June 2013. To aid diffusion, the company is offering special pricing programs in which patients can receive a free 15-day supply, for a reported savings of $100 (50% off the first month). Patients are eligible for savings of $75 per month if their health insurance copayment or out-of-pocket expense is greater than $50.[65]

Clinical trials: Lorcaserin's safety and efficacy have been investigated in three major clinical trials: Behavioral Modification and Lorcaserin for Obesity and Overweight Management (BLOOM),[66], Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM), and BLOOM in Diabetes Mellitus (BLOOM-DM).[67] The BLOOM study included 3,182 adults who were obese (BMIs of 30–45 kg/m^2) or overweight (BMIs of 27.0–29.9 kg/m^2) with at least one obesity-related comorbidity (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea). Patients were randomly assigned to receive either lorcaserin 10 mg twice daily or placebo twice daily. The authors reported the following results:[66]

> At 1 year, 55.4% of patients (883 of 1595) receiving lorcaserin and 45.1% of patients (716 of 1587) receiving placebo remained in the trial; 1553 patients continued into year 2. At 1 year, 47.5% of patients in the lorcaserin group and 20.3% in the placebo group had lost 5% or more of their body weight (P<0.001), corresponding to an average loss of 5.8+/-0.2 kg with lorcaserin and 2.2+/-0.1 kg with placebo during year 1 (P<0.001). Among the patients who received lorcaserin during year 1 and who had lost 5% or more of their baseline weight at 1 year, the loss was maintained in more patients who continued to receive lorcaserin during year 2 (67.9%) than in patients who received placebo during year 2 (50.3%, P<0.001). Among 2472 patients evaluated at 1 year and 1127 evaluated at 2 years, the rate of cardiac

> valvulopathy was not increased with the use of lorcaserin. Among the most frequent adverse events reported with lorcaserin were headache, dizziness, and nausea. The rates of serious adverse events in the two groups were similar.

In the BLOSSOM trial, 4,008 patients (aged 18–65 years, with BMIs of between 30 and 45 kg/m^2 or from 27.0 to 29.9 kg/m^2 with an obesity-related comorbid condition) were randomly assigned in a 2:1:2 ratio to lorcaserin 10 mg twice daily (BID), lorcaserin 10 mg once daily (QD), or placebo. All patients received diet and exercise counseling. The authors of the study reported the following:[68]

> Significantly more patients treated with lorcaserin 10 mg BID and QD lost at least 5% of baseline body weight (47.2 and 40.2%, respectively) as compared with placebo (25.0%, P < 0.001 vs. lorcaserin BID). Least squares mean (95% confidence interval) weight loss with lorcaserin BID and QD was 5.8% (5.5-6.2%) and 4.7% (4.3-5.2%), respectively, compared with 2.8% (2.5-3.2%) with placebo (P < 0.001 vs. lorcaserin BID; least squares mean difference, 3.0%). Weight loss of at least 10% was achieved by 22.6 and 17.4% of patients receiving lorcaserin 10 mg BID and QD, respectively, and 9.7% of patients in the placebo group (P < 0.001 vs. lorcaserin BID). Headache, nausea, and dizziness were the most common lorcaserin-related adverse events. U.S. Food and Drug Administration-defined echocardiographic valvulopathy occurred in 2.0% of patients on placebo and 2.0% on lorcaserin 10 mg BID.

The BLOOM-DM trial evaluated 604 patients (aged 18–65 years) with glycated hemoglobin (commonly known by its abbreviated form, HbA_{1c}) of between 7% and 10% and BMIs between 27 and 45 kg/m^2. They were treated with metformin or a sulfonylurea drug or both. Patients received diet and exercise counseling and were randomly assigned in a 1:1:1 ratio to placebo, lorcaserin 10 mg once daily, or lorcaserin 10 mg twice daily. The authors of the study reported the following:[67]

> More patients lost ≥5% body weight with lorcaserin BID (37.5%; p<0.001) or lorcaserin QD (44.7%; p<0.001) vs. placebo (16.1%; modified intent to treat/last observation carried forward). LSmean (±sem) weight change was -4.5±0.35% with lorcaserin BID and -5.0±0.5% with lorcaserin QD vs. -1.5±0.36% with placebo (p<0.001 for each). HbA1c decreased 0.9±0.06 with lorcaserin BID, 1.0±0.09 with lorcaserin QD and 0.4±0.06 with placebo (p<0.001 for each); fasting glucose decreased 27.4±2.5 mg/dL, -28.4±3.8 mg/dL and 11.9±2.5 mg/dL, respectively (p<0.001 for each). Symptomatic hypoglycemia occurred in 7.4% of patients on lorcaserin BID, 10.5% on lorcaserin QD and 6.3% on placebo. Common adverse events were headache, back pain, nasopharyngitis, and nausea. Lorcaserin was associated with significant weight loss and improvement in glycemic control in patients with type 2 diabetes.

With the approval, FDA required that the manufacturer conduct six postmarketing studies, including a long-term cardiovascular outcomes trial (CVOT) to assess the effects of the drug on the risk of major adverse cardiac events such as heart attack and stroke.[69]

The manufacturer planned to start CVOT in the second half of 2013, with anticipated completion in 2017 and final reporting by the end of 2018.[70] It also has plans to investigate lorcaserin in combination with phentermine and metformin.[70]

Manufacturer and regulatory status: Arena Pharmaceuticals, Inc., of San Diego, CA, makes lorcaserin. It submitted a new drug application (NDA) to FDA in December 2009 for lorcaserin for weight loss, weight management, and weight-loss maintenance.[71] In 2010, Arena licensed lorcaserin to Eisai Co., Ltd., of Tokyo, Japan, via its U.S. arm, for marketing and distribution in the United States for treating obesity. In September 2010, an FDA Advisory Panel on Endocrinologic and Metabolic Drugs voted 9-5 against recommending approval of lorcaserin. In October 2010, FDA recommended that the final data from the BLOOM-DM study be reported and asked for an independent pathology report to show that the drug's increased cancer risk in rats does not translate into such risk in humans. In January 2012, Arena resubmitted the NDA;[72] on June 27, 2012, following release of the BLOOM-DM study results, lorcaserin became the first drug approved to treat obesity since 1999.[67,69,73] The approved indication is as follows:

> BELVIQ is indicated to be used along with a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of:
>
> - 30 kg/m^2 or greater (obese), or
> - 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, T2DM)
>
> Limitations of Use:
>
> - The safety and efficacy of co-administration of BELVIQ with other products intended for weight loss including prescription drugs (e.g., phentermine), over-the-counter drugs, and herbal preparations have not been established
> - The effect of BELVIQ on cardiovascular morbidity and mortality has not been established

Diffusion: Lorcaserin will compete with orlistat and phentermine-topiramate extended-release (Qsymia) as one of three FDA-approved drugs for obesity treatment. Lorcaserin's availability after its approval was delayed while DEA evaluated how to classify the drug.[73] On June 7, 2013, lorcaserin debuted as a schedule IV controlled substance.[74] This classification allows physicians, including general practitioners, to prescribe the drug electronically through local pharmacies for a three-month supply at a time, so logistical barriers to obtaining the drug are not expected.[74,75] DEA also ruled to permit the combined use of lorcaserin with phentermine, which could potentially accelerate the drug's weight-loss benefits and hasten its diffusion if proved safe.[74] Lorcaserin is expected to cost about $1,800 per year (less when special pricing programs from the manufacturer are considered), and some payers have announced they will provide coverage for treatment.[74] According to a report, utilization projections for lorcaserin for 2013 are between 200,000 and 500,000 patients.[74]

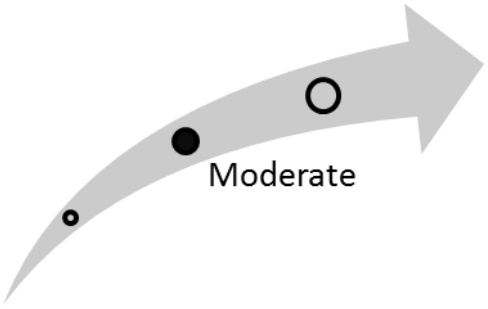
Two other broadly used nonselective serotonergic weight-loss drugs, fenfluramine and dexfenfluramine), were withdrawn from the market because of their association with cardiac valvular fibrosis and pulmonary hypertension when combined with phentermine (Fen-Phen).[76] Lorcaserin binds the same receptor as these drugs, and a fear of similar serious adverse events could slow lorcaserin diffusion, at least until data from the postapproval CVOT become available.[77]

Clinical Pathway at Point of This Intervention

Data suggest that at least 10% sustained total weight loss is needed to yield significant, positive clinical outcomes (e.g., reduce risk of diabetes, heart disease) in obese individuals.[78] Current weight-loss drugs fall short of this goal, and pharmaceutical companies continue to search for novel approaches to safe and effective weight-loss therapeutics, including using or combining with drugs previously approved for indications other than obesity.

Previous attempts to regulate appetite through serotonin pathways resulted in serious adverse events.[76] Serotonin and noradrenaline reuptake inhibitors fenfluramine and dexfenfluramine were both shown to significantly induce weight loss by decreasing meal intake and eating rate when coupled with phentermine (a combination commonly known as "Fen-Phen").[76] However, this resulted in heart valve disease, pulmonary hypertension, and, in some cases, death. Some researchers suggest that these adverse events result from nonspecific, serotonin-agonist binding to 5-HT2 receptors, especially 5-HT2A and 5-HT2B, which are linked to hallucinations, heart valve disease, and pulmonary hypertension.[76] Lorcaserin is purportedly a "full" 5-HT2C receptor agonist that binds 18 times as effectively as the 5-HT2A receptors and 104 times as selectively as the 5-HT2B receptors. As such, lorcaserin is a new serotonergic drug candidate that purportedly provides a nonsurgical alternative to obese patients after diet and exercise has failed.

Figure 4. Overall high-impact potential: lorcaserin (Belviq) for treatment of obesity



Experts commenting on this drug agreed that obesity is a major public health problem and that diet and exercise alone have historically been ineffective for maintaining weight loss. Lorcaserin's availability will expand the market for antiobesity drugs; obesity continues to be a condition for which efficacious pharmacotherapy is needed. Experts agreed that lorcaserin's impact potential will depend heavily on the drug's efficacy, with one research expert pointing out a need for clinical studies that directly compare lorcaserin to available oral antiobesity therapy. Some experts described the available data on lorcaserin as "encouraging" and "effective," adding that monitoring patients taking the drug, even after its FDA approval, is an important consideration moving forward. Two other broadly used nonselective serotonergic weight-loss drugs, fenfluramine and dexfenfluramine, were withdrawn from the market because of their association with cardiac valvular fibrosis and pulmonary hypertension. Because lorcaserin binds the same receptor as these drugs, a fear of similar serious adverse events could slow lorcaserin diffusion, at least until postapproval data become available. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on lorcaserin.[79-85] Please note that at the time they provided comments, FDA had not yet granted lorcaserin marketing approval. We have organized the following discussion of expert comments by subject.

Unmet need and health outcomes: An important unmet need for treating obesity exists, most experts agreed, saying that lorcaserin has potential to provide a nonsurgical treatment option for patients when diet and exercise strategies have failed. One clinical expert cited the BLOOM study, stating that "lorcaserin in combination with behavior and lifestyle management has been shown to significantly reduce body weight, and has few side effects." However, an expert with a research background pointed out that "results from completed clinical trials have been inconsistent." Basing their opinions on available clinical data, some experts thought that lorcaserin has a modest effect on weight loss but that whether the drug is sufficient to achieve sustained weight loss or improvements in comorbidities is inconclusive. Experts also highlighted the need for postapproval studies.

There is no "efficacy comparison with existing oral drug therapy for obesity," one research expert pointed out. However, data from at least one study suggests lorcaserin may not increase cardiac valvular disease occurrence (over placebo), an expert with a health systems and administration background pointed out, noting this is "an important observation given the problems associated with previous anti-obesity medication," adding that the potential of patients developing hypoglycemia with lorcaserin treatment warrants further review. According to one research expert, "compared to current treatment methods, lorcaserin seems to provide the most upsides with the least amount of side-effects," but there are "a lot of competitors in development." It should be noted that the competing antiobesity drug combination phentermine-topiramate had not received its July 2012 FDA marketing approval at the time experts submitted their comments.

Acceptance and adoption: In regards to acceptance, experts were optimistic about how patients and clinicians would view lorcaserin if it demonstrates safety and efficacy in a majority of patients. One research expert pointed out that "weight loss drugs seem popular [as] a first-line medical effort," and another expert with a health systems and administration background thought that "an oral medication taken once or twice a day with few side effects would be readily accepted by patients." According to a clinical reviewer, "based on past experience with FenPhen and sibutramine, clinicians are likely to accept lorcaserin if the drug is shown to be effective in the long term and does not have serious adverse effects, e.g., valvulopathy, neuropsychiatric disorders, and tumorigenesis." At the time of review, DEA had not yet announced whether it would classify lorcaserin as a Schedule III (i.e., drugs with a moderate to low potential for physical and psychological dependence) or schedule IV drug or permit lorcaserin to be combined with phentermine.

According to a clinical expert, lorcaserin is easy to prescribe, requires minimal patient education, and patients "may be more compliant with a pill [than with injection]." However, an expert with a research background noted that only a small percentage of obese patients actually seek treatment, and that "the public needs a proper education about obesity and the treatments there are available to them" in order to increase patients' willingness to accept lorcaserin.

Health care delivery infrastructure and patient management: Overall, lorcaserin has minimal potential to disrupt health care processes, the experts agreed. One expert with a health systems and administration background thought that "the availability of an effective

medication that can be prescribed by primary care providers in an outpatient setting and taken orally with few side effects sounds like an excellent intervention." However, the same expert pointed out that "health care providers as well as the FDA need to continue monitoring such patients closely in order to identify potential health problems which have arisen with other 'miracle' weight loss drugs (e.g., phen/fen)." Some experts thought that if lorcaserin is effective, it could reduce the need for other medication or complicated procedures needed to treat obesity.

Commenting on cost, experts agreed that if lorcaserin fulfills its intended medical purpose, it could substantially reduce the cost burden of treating obesity-related complications.

Health disparities: According to experts, lorcaserin is unlikely to affect health disparities. However, an expert with a health systems and administration background pointed out that health disparities would be affected by economic issues, such that "a considerable stumbling block needs to be overcome including access of such patients [African-American, Hispanic and American Indian populations in which oftentimes significant health care disparities exist] to health care providers as well as ability to purchase the medication [lorcaserin]."

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